Transcript: Wisdom for Women: An Expert's Take on HIV and Gender Differences

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At the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Peter Staley asks Dr. Sharon Walmsley what women need to know about HIV and antivirals; how the drugs work differently in women than they do in men; and gender differences needing more research. To see the video click here.

Peter Staley: Welcome, this is Peter Staley with AIDSmeds.com, and we're doing another interview here at ICAC 2007 in Chicago. We're once again in the "PharmaFest" area, the exhibit hall, where all the pharmaceuticals have their booths. And today we're going to be talking with Dr. Sharon Walmsley. You're Professor of Medicine at University of Toronto and assistant director of the Immunodeficiency Clinic in Toronto. So I guess you actually treat lots of people with HIV, is that correct?

Dr. Sharon Walmsley: Yeah, it's both, I'm a clinician and a clinical researcher, and I think those things go hand in hand, because you learn the very important questions for your research from the patients in your practice. So I do both.

PS: And you run the clinical trials network there?

SW: That's right, we are one of the sites of the Canadian HIV Trials Network, and I run the clinical research in our clinic.

PS: And your expertise is largely focused on women and HIV, and we're going to be talking a lot about that today. How did you get interested in that? Do you have a lot of women in your practice?

SW: Yeah, well obviously for your gender, women like to come to women, and I'm one of the only few women treating HIV, not only in Toronto, but in the world. And so yes, by nature, a lot of women came to my practice and clearly had some specific issues that we decided to make sure to address in our clinical research.

PS: A lot of people in our audience might not know that HIV reacts differently in women in certain ways, and so do the drugs, and we're going to cover both those areas. Let's start with the biological considerations. Viral load acts differently in men and women.

SW: Well, it's not that viral load *acts* differently, it's when you look at viral loads in women, particularly when the T-counts are within the normal range or in the high range—women,

compared to men—their viral loads tend to be a little bit lower. So let's say for example if you looked at somebody with a T-count of 500, the average viral load in men might be 50,000. The average viral load in women might only be 25,000. But as HIV progresses and as the CD4 count gets lower, then that difference between the two genders disappears. And I think what the challenge is is what does that mean, and why is it happening? And people have obviously implicated hormonal levels as to why that might be different. But the bigger concern is should we therefore change our guidelines for the initiation of treatment in women? And at the current time we don't because most the guidelines suggest we use T-count rather than viral load as the main reason to choose therapy, but we often use the viral load in concert with the T-count. And so I think we have to be aware of the fact that a viral load in women in a higher T-count may be a little lower than that of men.

PS: So how would that play out in terms of when to start?

SW: Well, again I think most of the guidelines now tell us that we should start antiretroviral therapy between 200 and 350, and it's, in that range, how do you decide? So often we use the viral load in that setting. So if the viral load is very high, we might tend to start HIV therapy more towards the 350 number, whereas if the viral load is lower, we might start more around the 200 level. I think what that means for women is that we really need to think that that viral load really isn't the same, and so our parameters for starting treatment in women might be moved up a little bit higher regardless of the viral load.

PS: I see. So if their viral load was showing lower than a man's would at that T4 range, they still might be considered...

SW: More likely to be considered than the man, to start.

PS: Exactly. Let's talk about the pharmacokinetic differences with the drugs. Obviously, we swallow them, they get absorbed in the stomach, and then they're distributed in the body. All that can be different in women than in men. Can you explain that?

SW : Yeah. I think that's sort of a question that a lot of my women have raised all the time and we in fact are doing a study right now to try and address this. We use the same dose. If you're 100 kilos and you're a man or you're 40 kilos and a woman, we use the same dose and I think intrinsically, all of us think, Is that right? So the difference is, women— first of all, women tend to be a little bit smaller. The amount of fat in their bodies unfortunately tends to be a little bit higher and the enzymes that metabolize or break down our medications or excrete our medications are different than those in men. And so what that all may translate into is that the doses of drug—standard doses—may result in higher levels of drug in women than in men. And although that may be good, because maybe women respond better to treatment if they have higher levels, it may also be bad if those are connected to toxicity. So that in fact is a study that we're doing across Canada right now. We're taking women, we're measuring the amount of drug in their system and trying to correlate that with adverse events to see if maybe we should be adjusting doses in women to try and minimize those effects.

PS: Now, have there been studies showing actual higher levels in the blood or in the cells of certain drugs in women as opposed to men?

SW: Yeah, unfortunately the literature is not very good, it's not very big despite 50% of people with HIV are women now. Studies have shown that for the protease inhibitors, saquinavir and ritonavir are higher in women than in men. For the non-nucleoside inhibitors, the levels of nevirapine are higher in women than in men. For the reverse-transcriptase inhibitors, drugs like 3TC and AZT are higher in women than in men.

PS: Retrovir, Epivir, which is Combivir in combination…

SW: Right, exactly.

PS: Let's end with a discussion of how this all plays out in the real world with the current antiretrovirals. What data do we have on some on the toxicities, how these play out differently in women than they do in men?

SW: Well, I think that first of all, we need to get women to participate more in trials. That's the problem—when we look at these studies, less than 10% sometimes are women. So how can we be sure that these things are as good in women or have more side effects in women?

PS: I understand that there's been a look at trials, and the percentage of women in trials in general has only been 12%.

SW: That's right.

PS: It's crazy. And this is something that AIDS activists have been screaming about from day one. I go back to the ACT UP days, and we were screaming about it then.

SW: Well, I think that early in the epidemic, it just reflected the fact that there were more men with the disease in North America than there were women. But times have changed now and it's greater numbers. So yes we need to find ways to encourage women to be part of trials, not to be afraid, and to provide services to help them look after their children or their jobs or whatever so that they can participate in trials. The other thing that drives women crazy is that when they participate in trials there has to be about nine different forms of contraception, and that can often be a burden, and, you know, we have to find ways to make those things easier. That being said most of the data would suggest that HIV medicines work as well in women as in men but it does appear for all classes of drugs that women have more side effects. So it's been shown with the proteases, it's been shown with the non-nucleosides, it's been shown with the reverse transcriptase inhibitors, toxicities in all those families are higher in women than in men, and although we don't definitively know why, you can't help but think that it has to do with the amount of drug in their system.

PS: And some of these have translated into—a few of these have translated into label changes like Viramune as far as when to start, there's a black box warning on your CD4 count, and it's different for men and women.

SW: Right. So with Viramune, which is a nevirapine, it's really been shown. So in terms of what we call the hypersensitivity reaction, which is the fever and the inflammation of the liver, it is clearly higher in women than in men and it clearly relates to the T-count. So women whose T-counts are greater than 250 or men whose T-counts are greater than 400, the risk of this reaction is huge. So there's a black box warning that we shouldn't use that drug in this circumstance. On the other

hand, if the drug is used safely, so if women have T-counts less than 250 or men have T-counts less than 400, then the risk of this problem is very, very small. So I think it's important that we learn more about these drugs and who is at risk for the side effects so that we can apply these safety measures to ensure that people aren't having problems from their drugs.

PS: Do you do any dose adjustments with women, going off-label?

SW: Well, you know, dose adjustment has not been recommended and in my country it's not covered, so it's really an issue, and I think that's partly why we're doing the study that we are right now, to try and determine whether or not we should be dose-adjusting in women who are having side effects. Now the down-side of that is that you don't want to make the level too low, that the drug doesn't work as well. So that's the balance.

PS: Well, thank you very much. This is a much-needed area of research; it's been needed from day one, and I'm glad you're doing that very important study on drug levels. Let's hope we get some good answers.

SW: Thank you very much.
